NOTE: Still open, last updated 7/12/01.

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OFFICE OF RESEARCH AND DEVELOPMENT
HEALTH SERVICES RESEARCH AND DEVELOPMENT SERVICE (HSR&D)

PROGRAM ANNOUNCEMENT: HIV/AIDS

VA QUERI
Quality Enhancement Research Initiative

Investigator-Initiated Research Priorities in HIV/AIDS

1. Purpose. The Veterans Health Administration (VHA) is focusing major resources and energy to improve the quality of the health care it provides and to create improvements that are measurable, rapid and sustainable. With the inauguration of the Quality Enhancement Research Initiative (QUERI) in early 1998, special emphasis has been placed on improving the quality of care in ten clinical areas that are prevalent in the VA: chronic heart failure, ischemic heart disease, diabetes, prostate disease, stroke, substance abuse, mental health (depression, schizophrenia), spinal cord injuries, HIV/AIDS, and cancer. For each of these areas, QUERI will identify gaps in science, practice, and information systems, and develop and evaluate methods for translating evidence of clinical effectiveness into practice. Additional information about QUERI is available on the VA web page at http://www.va.gov/resdev.

2. Synopsis. This announcement invites research proposals to enhance the quality of care for veterans with Human Immunodeficiency Virus (HIV)/ Autoimmune Deficiency Syndrome (AIDS) in two areas: a) assessment of practice patterns and innovative programs for identifying established and acute HIV infection among veterans; and b) improved measurement, assessment, and evaluation of interventions to improve adherence to antiretroviral medications in patients being treated for HIV. Projects may not exceed four years or total costs of $750,000. However, HSR&D is especially interested in projects that can demonstrate results promptly and efficiently. For example, descriptive studies or studies that do not include evaluation of a screening program or intervention would be expected to reach completion within two years, at a substantially lesser annual cost. For the initial round of review, a brief planning letter (see Attachment A) must be received by December 10, 1998 and full proposals must be received by February 5, 1999. The first opportunity for proposal review will be March 1999, with the earliest possible funding date of April 1999. Thereafter, projects will require a Letter of Intent consistent with regular IIR policy, and proposal due dates are May 1 and November 1, until further notice. These investigator-initiated research projects comprise part of a broader, comprehensive and merit-approved strategic plan that also includes a targeted research solicitation for service directed research projects to: validate and enhance the VA's HIV/AIDS registry and assess the quality of HIV care in VHA. [See "Service Directed Research to Improve HIV/AIDS Data and Assess VA HIV Therapy" at http://www.va.gov/resdev/hsr-sols.htm.] Investigators interested in HIV quality of care also should consider two solicitations for research that cuts across the conditions identified in paragraph one above. Specifically, HSR&D is issuing announcements entitled "QUERI: Common Issues in Implementation of Clinical Practice Guidelines" and "QUERI: Patient-Centered Outcomes," both available this month on the VA web page at http://www.va.gov/resdev/hsr-sols.htm.

3. Background. HIV disease is a substantial cause of morbidity and mortality in the United States. The Centers for Disease Control estimates that 650,000 to 900,000 Americans are infected with HIV, and disease due to HIV is responsible for about 8% of all years of potential life lost in the United States. The HIV Cost and Services Utilization Study (HCSUS) indicates that about 335,000, or less than half of these, are seen by a medical provider at least every six months, and that about 13%, or more than 40,000, of all those under care are veterans (Census Bureau, 1998). Extrapolation of VA's Immunology Case Registry data suggests that the Veterans Health Administration sees nearly 40% of all HIV-infected veterans (Bozette et al., in review). Since optimal care for HIV-infected persons can cost up to $30,000 per year per patient, and since sub-optimal care is associated with more rapid progression to significant (and expensive) complications, VHA has a substantial clinical and financial stake in quality of HIV care (Palella et al, 1998; Census Bureau, 1998).

Great strides have been made in the management of HIV. Many opportunistic complications now are largely preventable using chemoprophylaxis, and episodes that do occur generally cause much less morbidity and mortality than in the early days of the epidemic. The greatest improvements have come in the treatment of HIV itself. The ability to measure HIV activity directly with viral load testing and to often suppress viral replication with highly active combination antiretroviral regimens have revolutionized treatment. These regimens however include an expensive and difficult-to-use protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. They are difficult to use because of a high incidence of adverse interactions with other drugs and because they require patients to adhere carefully to dosing schedules or risk viral resistance and treatment failure. Nevertheless, these therapies have diffused rapidly in the HIV-infected population: during 1996, use rose from one-sixth to one-half of the population under care (Census Bureau, 1998).

Many efforts to help providers and patients manage these drugs have emerged. One prong of these efforts consists of panels to generate and promulgate guidelines for HIV care. Two of the most prominent sets of guidelines are from the International AIDS Society and the Department of Health and Human Services' Advisory Panel on Care for HIV Disease. Both of these groups have prominent VHA representation, and the VHA Technical Advisory Board for HIV/AIDS has recommended adaptation of the DHHS guidelines for use in veterans (CDC,1998).

Quality of and access to HIV care appear to vary significantly across HIV-infected populations and persons. Several studies have shown deficiencies in care and outcomes by demographic characteristics such as race, as well as by institutional and individual provider experience (Chaisson et al.,1995; Kitahata et al.,1996). The nationally representative HCSUS cohort has shown that deficiencies in access to care for HIV are common even among those in regular care. Seventy-three percent of persons under care had an unfavorable result for at least one of six access measures studied (Shapiro et al.,in review).

4. Research Priorities. Experts advising the VA have identified two distinct high priority areas for investigator-initiated research related to HIV. These areas are:

a) design and evaluation of programs to identify established and/or acute HIV infection among veterans; and

b) improved measurement, assessment, and evaluation of interventions to improve adherence to antiretroviral medications in patients being tested for HIV.

a. Design and Evaluation of Programs to Identify Established and/or Acute HIV Infection among Veterans

Diagnosis of ***established HIV infections*** is critical for interventions aimed at reducing the morbidity and mortality of HIV diseases. Identification of established HIV infection (defined as positive HIV antibody tests) enables providers to begin appropriate antiretroviral therapy (CDC, 1998), to start prophylaxis for opportunistic infections (CDC, 1997), and to provide counseling regarding reduction of risk behaviors (Owens et al, 1996). Counseling to reduce risk behaviors, when effective, provides a substantial public health benefit. Despite the clear individual and public health benefits from identification of people with HIV infection, findings from the HCSUS suggest that many people with HIV have not been identified and are not receiving appropriate care (Bozzette et al., 1998). The heavy burden of HIV disease among veterans suggests that population-based screening deserves consideration, as well as targeted testing based on elicitation of risk behaviors. Current guidelines recommend screening for HIV in acute-care hospitals with prevalence of greater than 1% (CDC,1993).

Detection of ***acute HIV infection*** (defined as a positive viral RNA with negative HIV antibody enzyme immunoassay) is a rapidly emerging priority. Fifty to 90% of people acutely infected with HIV are symptomatic (Kahn et al., 1998; Kinloch-de Loes et al., 1993; Schacker et al., 1996; Vanhems et al., 1997). However, because the symptoms are non-specific, acute HIV infection is often misdiagnosed as the "flu" in primary care settings. Antiretroviral treatment during acute infection reduces viral load and may mitigate loss of CD4 cells (Lafeuillade et al., 1997). Although there are no long-term clinical outcome data that show benefit from antiretroviral treatment during acute HIV infection, because CDC guidelines recommend treatment for symptomatic patients (Owens & Nease, 1997), acutely infected patients are candidates for therapy. Clinicians should counsel individuals with acute HIV infection to reduce risk behaviors, refer these individuals to appropriate research studies, and consider immediate antiretroviral therapy.

HSR&D Service therefore is interested in projects designed to:

1) Assess existing practice patterns for the identification of established and/or acute HIV infection.
2) Identify barriers to implementation of effective programs to identify established and/or acute HIV infection within the VA.
3) Evaluate the cost and cost effectiveness of proposed programs to identify established and/or acute HIV infection.
4) Develop the evidence base for recommendations for
    a) HIV screening to identify veterans who have established HIV infection, with particular attention to whether differences in patient populations or practice settings warrant different approaches and/or
    b) identification of acute HIV infection in veterans.
5) Implement and evaluate a demonstration project to assess the cost and cost-effectiveness of a program to identify veterans with established and/or acute HIV infection.

An evaluation of existing practice patterns should determine whether VA healthcare systems have implemented strategies to identify established and/or acute HIV infection, and whether the programs are effective. An evaluation should assess whether there are barriers to effective implementation of such programs. For example, potential barriers might include lack of primary care provider knowledge or lack of access to diagnostic tests and/or consultation. If feasible, investigators should compare how practices at VA healthcare systems compare to existing benchmarks and practice patterns outside of VA. Determination of effectiveness should include an assessment of the pertinent clinical and supportive services available for veterans.

Investigators also may propose demonstration projects that develop and implement programs to identify veterans who have established and/or acute HIV infection. These projects should build on the results of previous assessments, and use or modify (if appropriate based on evidence) established guidelines for HIV screening. Each such demonstration should include an assessment of the cost effectiveness of proposed interventions (including provider education and referral if appropriate) to identify individuals with established and/or acute HIV infection in VA healthcare systems. A project also might investigate whether differences in patient populations (such as the prevalence of HIV infection) lead to substantial differences in the cost effectiveness of such programs, and the need for differing recommendations. Project results could provide evidence for suggested modifications for VA use, if appropriate, of published guidelines.

b. Adherence to Antiviral Therapies for HIV/AIDS

Multi-drug highly active antiretroviral regimens have dramatically improved HIV therapy, and have led to declines in HIV-associated morbidity and mortality (Palella et al., 1998). As a consequence, national guidelines recently have been developed and disseminated that recommend using highly-active antiretrovirals in symptomatic patients with HIV, and in asymptomatic patients who have significant viremia or immunocompromise (CDC, 1998). Therefore optimizing antiretroviral treatment in all veterans with HIV clearly is central to any HIV/AIDS quality of care agenda. However with expanding use of highly active regimens in VA care settings, adherence to antiretrovirals is likely to become a significant problem that will lead to clinical failures, and potentially to public health risks (Williams et al., 1997; Wainberg et al., 1983; Montaner et al., 1998). HIV-infected veterans who do not take prescribed drugs correctly are likely to do poorly, since decreased drug exposure will permit ongoing viral replication and consequently lead to increased plasma levels of HIV, and to selection of resistant and possibly multi-resistant strains of HIV (Montaner et al., 1998; Shafer, et al., 1998; Wong et al., 1997). Resistant strains may in turn be transmitted sexually to others, with dire consequences for the public health as well as for the individual patient (Hecht et al., 1998). Patient, clinical, and system factors that most strongly influence adherence to antiretroviral medications are all poorly understood. HSR&D Service therefore seeks to stimulate investigator-initiated research projects to:

1) Evaluate, compare, validate, and improve methods for measuring antiretroviral adherence in patients using antiretrovirals to ensure accurate, accepted, and appropriate measures for research and clinical care applications;

2) Assess rates of adherence to antiretroviral therapies among veterans who receive treatment, and determine which individual, environmental, health, and regimen factors are most strongly associated with adherence and with consequent viral suppression;

3) Evaluate interventions for improving adherence to antiretroviral medications in patients being treated. Evaluations are expected to include identification and assessment of successful programs now in use for improving and sustaining adherence among veterans, as well as design and evaluation of new adherence programs, with attention both to proximal effects on adherence, and to distal effects on viral load, resistance patterns, incidence of opportunistic diseases, and prevention of hospitalizations.

Projects addressing adherence to antiviral therapies for HIV/AIDS should address one or more of these three general adherence research domains, described in more detail below. Proposals

may be limited to in-depth investigation of one of the areas (for example, development of adherence measurement methods), or they may contribute to each of the three areas in an effort to assess, understand, and improve antiretroviral adherence in veteran populations. Projects that set out to improve methods of adherence measurement should consider that adherence will be measured as a key outcome and mediating variable in clinical research, and that adherence measurement may be introduced directly into clinical care to guide patient teaching and clinical decisions. Projects describing adherence and its correlates should explore the links between adherence and both clinical and new/emerging biological outcomes of significance, such as viral load suppression and the development of drug-resistant HIV strains.

While recognizing the importance of improving assessment methods for antiretroviral adherence and of describing factors associated with adherence, the HSR&D Service anticipates the possibility of moving ahead rapidly with carefully-designed, quasi-experimental studies to evaluate promising programs already in use, as well as creating and evaluating experimentally new programs rooted in theory and in emerging empirical data*. Proposals to simply collect longitudinal data from participants in new adherence programs without comparison groups will not be considered responsive to this request.*

1) Improving *Measurement of Antiretroviral Adherence*. Many methods of measuring patient drug-taking behaviors have been used in adherence research, but there is no true "gold standard" for assessing adherence (Besch, 1995; Gordis, 1979; Ickovics & Meisler, 1997). Methods of adherence assessment frequently used in research include: patient *self-reports* in questionnaires, interviews, or diaries; *pill counts* conducted during clinic visits or home visits (comparisons of numbers of tablets dispensed minus returned with the number prescribed over an assessment interval); *plasma or urine active or "marker" drug levels* compared to expected levels; and *electronic monitoring methods* (such as the Medication Event Monitor System) in which computerized pill dispensers record and store the date and time of each opening of a medication dispenser. Choice of a method often depends on the specific types of research questions being asked, and frequently on pragmatic considerations. Comparing the strengths and weaknesses of these various measurement methods, and improving on them, should be an important early part of the antiretroviral adherence research agenda.

2) Assessing *Antiretroviral Adherence.* A full description of antiretroviral adherence among veterans in clinical care will include measurement of adherence rates, and assessment of both the determinants and outcomes of good adherence. The factors that influence adherence are likely to fall into several domains. Among the areas considered important are the following: patient-*specific factors*, including sociodemographic, economic, psychological, attitudinal, knowledge, clinical status, and behavioral variables; *provider-specific factors*, such as training, practice style, specialization; *characteristics of the patient-provider interaction*, such as trust, communication, collaborative decision-making processes, communication skills, and language/cultural congruence; *regimen factors*, such as complexity and toxicity; *characteristics of the environment,* such as social, emotional, and financial support, and living arrangements; and *healthcare system and service delivery models,* such as use of case management, HIV care as a component of primary care (vs. "clinic" care), and integration of care in dually-diagnosed patients. Descriptive work is needed to determine the rates of adherence to antiretrovirals among veterans, and to determine which variables are the strongest predictors of adherence.

The outcomes of successful antiretroviral adherence are unknown, but may include known consequences of higher drug exposure, such as suppression of plasma viral load, and prevention of resistant HIV strains. Furthermore, antiretroviral adherence may be associated with maintenance of improved CD4+ lymphocyte counts, reduction in HIV-related opportunistic diseases, improved physical function, and lower hospitalization and health service utilization rates.

3) Evaluating *Interventions for Improving Adherence.* While the earliest adherence research within the VA should be to describe antiretroviral adherence, the body of research on interventions in other

chronic diseases should serve as a basis for prompt progress toward designing and testing antiretroviral adherence interventions (Haynes et al., 1996). And because many programs for improving and maintaining adherence are already in place in clinical settings, research that uses non-randomized designs to evaluate existing programs may make an important contribution, and should be considered. Nevertheless, experimental studies of carefully designed adherence interventions that are based on both theoretical models and empirical research will be extremely important.

5. Research Methods. Proposals developed in response to this announcement should use appropriately rigorous and efficient designs. Evaluations may use experimental, quasi-experimental or cross-sectional designs. Evaluations should consider compliance with testing recommendations among veterans, and the cost effectiveness of testing. Each proposal is expected to specify and justify the outcomes to be assessed in terms of their relevance to HIV quality of care and to explain how they will be defined, measured, and evaluated.

Demonstration projects submitted for this announcement must:

- focus on well-designed interventions with clear applicability to multiple VA sites,
- test explicit hypothesis(es) about the relationship between the intervention and specified outcomes, and
- include a well-designed plan for obtaining and analyzing the intervention's effect on costs and quality of care

6. Application Process.

a. Eligibility. Investigators who hold a VA appointment of at least 5/8 time are eligible to apply for research support. Co-investigators, consultants, and support staff may be non-VA employees. Refer questions about eligibility to Robert Small at 202/273-8256 or robert.small@mail.va.gov.

b. Planning Letter. A planning letter is the first step in preparing a proposal. It will be used only for administrative purposes (for format, see Attachment A). The usual Letter of Intent (LOI) process required for HSR&D's Investigator-Initiated Research projects, whereby a detailed description of the project must be approved prior to submitting a full proposal, **does not apply** to this solicitation. Planning letters are due at the address listed in paragraph 9 ("Inquiries"), by the close of business on December 10, 1998. Facsimile and electronic mail copies will be accepted; address these to John Francis, HSR&D Service, at FAX number 202/273-9007 or john.francis@mail.va.gov.

c. Proposal Preparation and Submission. For detailed instructions regarding preparation and submission of a full proposal, and general review criteria, applicants should refer to HSR&D's "Instructions for Preparing Investigator-Initiated research Proposals" (available at all VA research offices and on the VA research home page at http://www.va.gov/resdev). Full proposals must be received by February 5, 1999.

d. Review. The first set of proposals based on this announcement will be reviewed at the Scientific Review and Evaluation Board subcommittee meeting in March 1999. Starting in June 1999, and until further notice, such proposals will be reviewed at regularly scheduled meetings of the Board, along with other IIR projects. The review is rigorous and standards very high; both scientific merit and expected contribution to improving VA health services are considered. Investigators are expected to develop and describe their research plan completely and in detail. Proposals recommended for approval will be considered for funding.

7. Funding. Studies submitted in response to this solicitation may not exceed four years or total costs of $750,000. Both short-term and long-term projects may be proposed, but HSR&D is particularly

interested in projects that can demonstrate results in the shortest possible time. For projects that require more than two years, investigators are *strongly encouraged* to identify major milestones or project components for which interim results can be reported and published. In planning project budgets, applicants are reminded to adhere to R&D guidelines regarding allowable use of research funds for specific items. HSR&D expects to fund the first projects under this program in April 1999.

8. Coordination with QUERI. Principal investigators will submit regular annual progress reports and requested updates to the Director, HSR&D, who will provide these to the appropriate QUERI Coordinating Center, through the Associate Director for QUERI.

9. Inquiries. For further information about this solicitation, contact:

Shirley Meehan, MBA, PhD
Deputy Director
Health Services Research and Development Service (124A)
Department of Veterans Affairs
810 Vermont Avenue, NW
Washington, DC 20420
202/273-8287

John R. Feussner, M.D.
Chief Research and Development Officer

Attachment

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ATTACHMENT A

SAMPLE FORMAT FOR HSR&D PLANNING LETTERS

Provide a one-page letter addressed to the Review Program Manager (124F) that includes the following information:

1. Principal Investigator's name, affiliation, address, phone number, e-mail, and FAX number.

2. Name and affiliation of co-principal investigator, if applicable, and other key project participants.

3. Title and date of this solicitation.

4. Proposal title.

5. Specific focus of the proposed study.

6. Major methods to be used and type(s) of analyses to be performed.

7. (Optional) Name two or more scientists who are qualified to review the proposal; include name, degree, title, academic affiliation, complete address, telephone number, and e-mail address, if available.

8. Signature of the ACOS for R&D.